DRUG & ALCOHOL FINDINGS *Review analysis*

This entry is our analysis of a review or synthesis of research findings considered particularly relevant to improving outcomes from drug or alcohol interventions in the UK. The original review was not published by Findings; click Title to order a copy. Free reprints may be available from the authors – click prepared e-mail. Links to other documents. Hover over for notes. Click to highlight passage referred to. Unfold extra text The Summary conveys the findings and views expressed in the review. Below is a commentary from Drug and Alcohol Findings.

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▶ Pharmacologically controlled drinking in the treatment of alcohol dependence or alcohol use disorders: a systematic review with direct and network meta-analyses on nalmefene, naltrexone, acamprosate, baclofen and topiramate.

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In 2013 nalmefene was authorised for moderating drinking among patients not in need of detoxification, extending pharmacotherapy to less dependent drinkers. Though uniquely authorised for this purpose, this review found other (and probably cheaper) drugs have been just as or possibly more effective, but for none was there high quality evidence.

SUMMARY This review effectively assessed a range of medications for roughly the purposes for which nalmefene was granted marketing authorisation in Europe and approval in the UK – to help reduce consumption in alcohol-dependent adults who do not have physical withdrawal symptoms and do not require immediate detoxification, rather than as part of a treatment intended to sustain abstinence in detoxified patients.

Nalmefene's parent drug, naltrexone, is approved for maintaining abstinence, but has also been prescribed 'off-label' to moderate consumption. Other drugs acting on neural networks driven by the neurotransmitter gamma-aminobutyric acid have been studied for this purpose, including baclofen and acamprosate and the anti-epileptic topiramate. Widely disseminated guidelines and major reviews now promote medications to help moderate drinking as part of a harm-reduction strategy.

The featured review aimed to assess the efficacy of this approach in general, and the relative efficacy of the different medications, by amalgamating findings from head-to-head comparisons between these and from indirect comparisons via studies which have, for example, compared drug A and drug B with a placebo, but in different trials – so-called 'network' analysis.

An attempt was made to limit the selection of trials to non-abstinent patients who have not completed detoxification. As this is usually completed after five to seven days, trials were included which recruited patients abstinent for less than five days. Excluded were trials which stipulated longer abstinence periods or prior detoxification, and those which selected patients also suffering physical or psychological comorbidity.

Key points
From summary and commentary

In 2013 nalmefene was authorised for moderating drinking among patients not in need of detoxification, extending pharmacotherapy to less dependent drinkers.

The featured review examined whether other medications (naltrexone, acamprosate, baclofen, and topiramate) have been found to do this just as well among non-detoxified patients with an alcohol use disorder.

There was no high quality evidence for any the medications, though nalmefene, topiramate and baclofen have been found to reduce consumption, and topiramate also consistently reduced other measures of drinking. No evidence was found that nalmefene was superior to the other medications, or that any improved health.

To help eliminate bias, the trials had to have randomly allocated adult patients with a diagnosis of alcohol use disorders (including dependence) to one of the medications versus another medication, and/or versus an inactive placebo. Reports in English, French, German and Spanish were considered, retrieved in searches conducted up to June 2016. Unpublished studies and those conducted for pharmaceutical companies were also sought.

Of primary interest was the medications' impacts on total alcohol consumption, stemming from the rationale that if medications reduce consumption, they also correspondingly reduce alcohol-related harm. However,

other consumption outcomes were assessed, as were indications of the safety of the medications.

In the event, all 32 trials included in the amalgamation of results compared the medications with a placebo rather than with each other. Published between 1994 and 2015, nine compared of nalmefene with placebo, 14 naltrexone, four each baclofen and topimarate, and just one acamprosate. Except for one nalmefene and one naltrexone trial, all patients were offered psychological support (including medical management programmes) during the study periods.

Due to possible or actual loss to follow-up, 26 of the 32 studies were vulnerable to bias due to incomplete outcome data. Also, in 17 the researchers had not registered their analysis plans in advance, so outcomes might have been selectively reported.

Main findings

Of the 32 studies, only half reported total alcohol consumption; for acamprosate and baclofen there was just one study each, and for topiramate, two. Across all relevant studies, consumption was reduced significantly more when patients had been allocated to nalmefene, topiramate or baclofen than to a placebo. This was not the case for naltrexone and acamprosate.

More (21) studies reported the number of days on which patients drank heavily, but for acamprosate there were none. As with consumption, heavy drinking was reduced significantly more when patients had been allocated to nalmefene or topiramate than to a placebo, but on this measure baclofen as well naltrexone had not been shown to be effective. Additionally, compared to a placebo topiramate significantly increased the number of non-drinking days and nalmefene reduced the number of drinks per drinking day.

For nalmefene, all estimated effect sizes were small, while baclofen registered a large effect on total consumption but varied effect sizes on other measures. Topiramate consistently showed medium to large effect sizes on all drinking outcomes.

In different studies results for naltrexone and topiramate substantially varied. In particular, for naltrexone one study actually found a placebo significantly more effective.

None of the medications was associated with significantly more deaths or serious adverse events than a placebo. However, withdrawals from treatment for safety reason were more common among patients allocated to nalmefene and naltrexone, and adverse events in general more common for naltrexone.

The indirect ‘network’ comparisons had to rely on how the medications compared to a placebo; there were no direct comparisons between the medications with which to check the validity of these estimates, and variations between studies were substantial. On this rather unreliable basis, across all drinking outcomes topiramate seemed superior to nalmefene, naltrexone and acamprosate. In respect of total consumption, baclofen seemed more effective than naltrexone and acamprosate, but was not consistently superior on other measures. No significant difference was found across drugs on safety outcomes, except for withdrawals for safety reasons. These were generally more common on placebos than on active medications and less common on nalmefene than acamprosate, though there was just one study for the latter drug.

There was no evidence of differences in drinking outcomes between nalmefene and naltrexone and their safety profiles were similar.

The authors’ conclusions

While the extension of pharmacotherapy to less severely dependent or non-dependent drinkers is often advocated as a ‘paradigm shift’, the evidence clearly questions guidelines that promote this approach. No medication currently has high-quality evidence for moderating drinking among patients suffering from alcohol use disorders. At best, some have low to medium efficacy relative to a placebo, but across studies at high risk of bias. Though based on all the available data in the public domain, no evidence was found of better health outcomes in comparison with a placebo, though no study was of sufficient size and duration to investigate these outcomes. It should be borne in mind that pharmacological approaches which might benefit patients by reducing drinking might also harm them due to side effects. Outcomes which are surrogates for health – such as drinking amounts – should not be relied on as indicators of health outcomes. Trials should be required which are capable of directly assessing health outcomes, including adverse effects of medications.

The data suggests that topiramate could be the most effective treatment, with medium to large effect sizes on most consumption outcomes. However, we can only have very low confidence in this evidence, which should be considered a prompt to further exploration rather than definitive. In the analysed studies its safety profile does not appear to differ from that of placebo in respect of adverse events, serious adverse events, or deaths. However, from other studies we know topiramate can, for example, cause negative cognitive side effects such as deterioration in verbal fluency, language comprehension, and working memory. In the analysed studies topiramate may have seemed as safe as other drugs

because studies were too small, too short, or of insufficient quality to find harmful effects or events.

Regarding the primary outcome, nalmefene, baclofen and topiramate all reduced total alcohol consumption more than a placebo, while indirect comparisons suggested that topiramate was more effective than nalmefene, naltrexone or acamprosate. Nalmefene and naltrexone were associated with a significant increase in withdrawals from the study and withdrawals for safety reasons, raising concerns over biased outcomes due patients not being followed up.

Though promoted and authorised for the purposes investigated by the featured analysis, no evidence was found that nalmefene was superior to the other medications. Relative to a placebo, naltrexone and acamprosate had yet to be shown to be effective for these purposes. On baclofen these was only very poor evidence from small studies involving low doses (30–50mg a day); prescription of high doses (up to 300mg a day) has spread rapidly among alcohol specialists.

FINDINGS COMMENTARY It is important to be aware that the limitation to non-detoxified caseloads who may still be drinking when treatment starts excluded many studies from the featured analysis, most dramatically in the case of acamprosate, for which just one study was found despite a more inclusive review having found 22 trials whose results were published up to September 2013. This limitation may partly account for the lack of data on health-related outcomes, and means the review's findings of little evidence of safety differences may simply be due its limited remit.

The lead author and three of his six co-authors were also among the authors of a review critical of evidence which in 2013 led the European Medicines Agency to authorise nalmefene to reduce drinking among heavy drinkers who do not have physical withdrawal symptoms and do not require immediate detoxification. The decision paved the way to realising the hope that it will help tackle the bulk of dependent drinking lying below the iceberg-tip of physically dependent drinkers aiming for abstinence – and at the same time open up for the manufacturer Lundbeck a huge market previously all but closed to pharmaceutical solutions.

They acknowledged that among this type of patient, those allocated to nalmefene rather than a placebo drank slightly less, and severity of dependence and alcohol problems also improved more. However, when they accounted for patients lost to the studies by assuming they continued to drink as they did at the start of the trials, alcohol consumption outcomes were no longer significantly better among patients allocated to nalmefene.

Is nalmefene uniquely appropriate for this caseload?

The featured analysis can be understood as an attempt to establish whether nalmefene is unique in reducing drinking among these types of patients (if indeed it does), or only unique in a pharmaceutical company having sought and gained authorisation for this purpose. The latter seems to be the case. Our commentary on the nalmefene analysis had also concluded that naltrexone's effects compare well with nalmefene, and noted that in the only head-to-head comparison – a laboratory study – it led to roughly the same inhibition of drinking.

> *Is nalmefene unique in reducing drinking among these patients – or only unique in having gained authorisation?*

The significance of these conclusions is that, available as a generic product, naltrexone is much cheaper. If as the featured analysis and our earlier analysis found, it is no less effective and no less safe, across a relevant caseload there is no clinical justification for spending more to provide nalmefene, and the main reason for doing so would boil down the commercial decisions taken by pharmaceutical companies to seek or not seek authorisation for reducing drinking among not very heavily dependent drinkers.

Other drugs investigated in the featured review – acamprosate and naltrexone – are two of the three main medications licensed in the UK for the treatment of alcohol dependence and endorsed in national guidance for Scotland and England and Wales. Pharmacologists have argued that these and other medications should be offered to non-dependent problem drinkers who have not responded well to 'talking' therapies, an a practice which would extend their use into and beyonf nalmefene's territory.

Though the featured analysis finds no reason to prefer nalmefene, it also finds insufficient evidence to back prescribing any of the medications for a nalmefene-type caseload. For people who see dependent drinking as fundamentally a psychological and social problem, prescribing medications to this caseload represents an unwelcome extension down the severity range of an opposing vision of the condition as due to neurochemical processes correctable by drugs. Since

nearly all the trials accompanied medication or placebo with psychosocial support, the implication of the featured analysis is that none of the medications has definitively demonstrated its superiority to psychosocial support for this kind of caseload.

Topiramate leads the pack

Topiramate emerged as the most effective medication in reducing drinking across different measures and as safe as any other. As the authors point out, its apparent safety may be a function of the limitation to four studies and of the inadequacy of those and comparison studies for establishing health outcomes. However, this drug seems to have established itself as one to use when patients are still drinking and may not be aiming for abstinence, meaning relatively few studies were excluded from the analysis.

A review not limited to a nalmefene-type caseload and published in 2009 concluded that "topiramate shows great promise as a treatment for alcohol dependence", with moderate-size effects (most drugs have small effects) which appear to increase over time. There have, however, been commonly reported side effects which lead to excessive withdrawal from treatment, the most disturbing for patients being related to the depressant effects which come with topiramate's potent anti-convulsive properties. Also noted are sensory disturbances including interference with taste and uncomfortable skin sensations, as well as anorexia and other complaints. These unwanted effects are considerably reduced if the dose is gradually adjusted up to its maximum, allowing the reviewers judge that "topiramate has a favourable adverse event profile". Depressant effects also mean that the risk of dangerously reduced functioning is greater if the medication is taken with other depressant drugs, including alcohol.

Reviewers for the British Association for Psychopharmacology acknowledged the drug's impacts on drinking, but also noted that its "adverse event profile has likely limited clinicians using topiramate". They did however agree that many of these side effects were due to fast titration to high doses, noting that "slow titration to 300mg/day over 6–8 weeks has been advocated". Nevertheless, they still felt 300mg a day may be too high for some patients to tolerate.

Most pertinent for UK policy is the review undertaken for the National Institute for Health and Clinical Excellence, the basis for its recommendations on which medication should made available to National Health Service patients. Topiramate is not authorised or recommended in guidance for the treatment of drinking problems in the UK, and when they updated their review in 2013, the reviewers saw no reason to change the judgements which underpinned this decision.

This draft entry is currently subject to consultation and correction by the study authors and other experts.

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